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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/526,106	03/15/2000	Robert F. Balint	PARE.002.01US	9164

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/526,106	BALINT ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *2/6/2004*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/8/04 has been entered. Claims 63-66 were pending. Applicants amended claim 63. No claims were added or canceled. Therefore, claims 63-66 are still pending and active in the instant application. An action on the merit follows.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. The New Matter rejection under 35 U.S.C. 112, first paragraph is hereby withdrawn in view of Applicants' arguments and/or amendments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

3. Claims 63-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabled for non-mutant N-terminal β-lactamase fragments that are used in

complementation systems that contain an NGR tri-peptide, a $(Gly_4Ser)_3$ linker and a C-terminal β-lactamase fragment are not enabling for mutant N-terminal β-lactamase fragments (e.g., $55_{Lys\rightarrow Glu}$, $62_{Pro\rightarrow Ser}$ and $182_{Met\rightarrow Thr}$ mutations) that are used in complementation systems that contain any C-terminal fragment and any linker and any tri-peptide or other variant. This is an enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) Breadth of the claims and nature of the invention: The scope of the claim is broad because Applicant uses "comprising" terminology that would include an infinite number of sequences. Furthermore, applicants' claims encompass mutating said infinite number of sequences (e.g., $55_{Lys\rightarrow Glu}$, $62_{Pro\rightarrow Ser}$ and $182_{Met\rightarrow Thr}$ mutations) and using said infinite number of sequences in undisclosed complementation systems.

(3 and 5) The state of the prior art and the level of predictability in the art: The prior art teaches that protein aggregation, folding and binding interactions are inherently

unpredictable. It is known in the art that even a single amino acid change can have dramatic effects on the proteins' structure/function. For example, Voet et al. (1990) teach that a single Glu → Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic and blood flow blockages (see Voet, D. and Voet, J. G. Biochemistry. New York: John Wiley and Sons 1995, pages 126-128, section 6-3A and page 230, column 2, first paragraph). Here, Applicants' "comprising" language would include the addition of "amino acids" to the N- and/or C-terminal end of the fragment, which would have an unpredictable effect on the structure/function of the fragment. Furthermore, another layer of unpredictability would be added onto this by the claimed mutations (e.g., e.g., $55_{Lys \rightarrow Glu}$, $62_{Pro \rightarrow Ser}$ and $182_{Met \rightarrow Thr}$ mutations).

In addition, the prior art indicates that the claimed β-lactamase enzyme fragment would not function with all "complementation systems" i.e., only complementation systems that contain Asn-Gly-Arg tripeptide (NGR) and the $(Gly_4Ser)_3$ linker in addition to the complementary C-terminal β-lactamase fragment would be enabled (e.g., see Wehran et al, Abstract, "Critical to this advance [describing Applicants' claimed invention as exemplified in Example 6 of the specification] was the identification of a tri-peptide, Asn-Gly-Arg [NGR], which when juxtaposed at the carboxyl terminus of the α fragment increased complemented enzyme activity by up to 4 orders of magnitude") (emphasis on the word "critical") (Wehrman, T.; Kleaveland, B.; Her, J.-H.; Balint, R.F.;

Blau, H.M. "Protein-protein interactions monitored in mammalian cells via complementation of β-lactamase enzyme fragments" PNAS 2002, 99(6), 2469-3474). In this regard, it is noted that claims which lack critical or essential subject matter, which is necessary to the practice of the invention, but is not included in the claim(s), including essential compound structure, is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976); and *Ex Part Bhide* (Bd Pat. App. & Int.) 42 USPQ2d 1441.

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants disclose only examples of "non-mutant" N-terminal β-lactamase fragments that contain "interaction-dependent" activity (e.g., see Example 6 in specification). Furthermore, these "non-mutant" N-terminal β-lactamase fragments are coupled to essential tri-peptides like NGR, a $(Gly_4Ser)_3$ linker and a C-terminal β-lactamase enzyme fragment. For example, Applicants state, "However, for both mutants [i.e., referring to combinations of the currently claimed $55_{Lys\rightarrow Glu}$, $62_{Pro\rightarrow Ser}$ and $182_{Met\rightarrow Thr}$ mutations], plating efficiencies were just as high or higher in the absence of the heterolgous interaction i.e., with the jun helix removed. An exhaustive search for more mutations did not turn up any mutants with interaction-dependent activity. Thus, in contrast to the results obtained with random tri-peptides, where activation remained interaction-dependent, adaptive mutations of α197 invariably eliminated interaction dependents" (see specification page 48, lines 3-8, see more generally Example 7)

(emphasis added). Complementation systems, however, require "interaction-dependent" activity because without this activity the complementation system could not differentiate between test proteins that interact with one another from those that do not (e.g., the N-terminal and C-terminal fragments would come together regardless of whether the test proteins interact thus negating the usefulness of the complementation system).

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The Examiner contends that the quantity of experimentation needed to make and or use the invention would be great because Applicants specification provides evidence that the claimed invention will not work (see sections 6-7 above). In addition, Applicants have omitted essential subject matter (see sections 3 and 5 above). Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991).

Response

4. Applicant's arguments directed to the above Enablement rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Applicants have removed the 'comprising' language from claim 63" and, as a result, Applicants are now enabled (e.g., see 3/8/2004 Response, page 7, paragraph 1).

[2] Applicants argue that the Galarneau et al. scientific article provides evidence that those tripeptides are "not a critical feature" of the claimed invention and that Applicants are enabled for the claimed complementation system in vitro and in eukaryotic cells as demonstrated by said article (e.g., see 3/8/2004 Response, page 8, paragraphs 1-3; see also Exhibit A). Applicants also refer to MPEP § 2164.05 in support of the notion that all evidence before the Examiner must be considered (e.g., see 3/8/2004 Response, page 10, first full paragraph).

[3] Applicants state that their "generic language" found in the introduction to the specification "clearly contemplates the use of an oligopeptide ... such as M182T" (e.g., see 3/8/2004 Response, page 9, especially quotation of page 6, lines 5 to 9 of the specification wherein the "generic language" states, "Functional reconstitution of the fragment pairs into a marker protein can be enhanced by ... introducing 1-3 codon changes within the nucleotide sequence").

[4] Applicants argue that the Examiner must consider the "entire disclosure" with regard to a critical feature in accordance with MPEP § 2164.08(c) (e.g., see 3/8/2004 Response, page 9, last paragraph).

[5] Applicants argue, "The Examiner is respectfully reminded that claims 63-66 are drawn to an oligopeptide for use in a fragment complementation system, not the complementation system itself, and not a method of using the oligopeptide. By requiring Applicants to claim another component of the complementation system, the Examiner is

essentially denying Applicants the opportunity to claim any single component. If the Examiner's position were proper, inventors would be forbidden from claiming any individual component of a novel system. For example, a claim drawn to a novel carburetor for use in a novel engine would be rejected as failing to recite the essential component of the novel engine" (e.g., see 3/8/2004 Response, page 10, last two paragraphs).

This is not found persuasive for the following reasons:

[1] The Examiner contends that the "consisting essentially of" claim language is indefinite (e.g., see 35 U.S.C. 112, second paragraph rejection below) and, as a result, Applicants' arguments are moot.

[2] First, the Examiner contends that Applicants' arguments are not commensurate in scope with the claims. Galarneau et al. only teach the M182T mutant (e.g., see Michnick et al., page 619, column 2, second full paragraph; see also Applicants' admission in the 3/8/2004 Response, page 10, first full paragraph). Thus, Applicants' arguments are moot with respect to the currently claimed "lysine to glutamic acid" and "proline to serine" substitutions at positions 55 and 62, respectively.

In addition, the Examiner contends that Applicants' cited reference would not enable a person of skill in the art ***at the time of filing*** for even the M182T mutant because the Galarneau et al. reference was published in **June 2002**, which was approximately two years after Applicants' filing date i.e., **March 15, 2000**. If anything, the Galarneau et al. reference provides support for the Examiner's position because a prestigious journal like Nature would not allow an article to be published (i.e., in June 2002) if the material upon which the publication was based

(i.e., the use of mutants like M182T in the absence of a tripeptide) was already known in the art two years earlier (i.e., March 2000) when the application was filed.

[3] First, the Examiner notes that the cited passage in the specification (i.e., page 6, lines 5 to 9) does not refer to the M182T mutant nor does it refer to the K55E/P62S mutants and thus does not "clearly" contemplate such mutants (i.e., disclosure of a large and varied genus does not provide "clear" support for a single species). Second, when the specification does refer to the claimed M182T, K55E and P62S mutants, it states that these mutants ***do not work*** (at least with regard to "in vivo" applications using "prokaryotic" cells; see also Applicants' 3/8/2004 Response, page 9, second to last paragraph; see also specification page 48, lines 3-8, "However, for both mutants [i.e., referring to combinations of the currently claimed $55_{Lys \rightarrow Glu}$, $62_{Pro \rightarrow Ser}$ and $182_{Met \rightarrow Thr}$ mutations using a complementation system in vivo with prokaryotic cells], plating efficiencies were just as high or higher in the absence of the heterolgous interaction i.e., with the jun helix removed. An exhaustive search for more mutations did not turn up any mutants with interaction-dependent activity. Thus, in contrast to the results obtained with random tri-peptides, where activation remained interaction-dependent, adaptive mutations of α197 invariably eliminated interaction dependents" (emphasis added). Complementation systems, however, require "interaction-dependent" activity because without this activity the complementation system could not differentiate between test proteins that interact with one another from those that do not (e.g., the N-terminal and C-terminal fragments would come together regardless of whether the test proteins interact thus negating the usefulness of the complementation system).

Thus, absent any clear indication that the claimed M182T, K55E and P62S mutants would work *in vitro* using complicated eukaryotic systems, there is no reason to "assume" that

they would especially in light of Applicants' examples which explicitly disclaim their use *in vivo* using simple prokaryotic systems (e.g., see above). In other words, Applicants' own examples "teach away" from (or contradict) their generic language. For example, Applicants state "[a]ppropriate host cells for application of the subject invention include both eukaryotic cells, such as mammalian, yeast and plant cells, and prokaryotic cells, such as bacterial cell" (e.g., see specification, page 12, lines 6-9). However, this statement is false (at least in part) because the M182T, K55E and P62S mutants (outlined in Example 7) ***do not work*** in "prokaryotic cells, such as bacterial cell[s]" (e.g., see specification page 48, lines 3-8, see more generally Example 7 wherein Applicants contradict their own specification by stating, "An ***exhaustive search*** for more mutations [referring to the use of prokaryotic cells] ***did not turn up any mutants with interaction-dependent activity***"). In addition, there is no indication that these mutants would work *in vitro* using the more complicated eukaryotic systems. Thus Applicants' specification would impede (rather than enable) a person of skill in the art from pursuing mutants like M182T, K55E and P62S in vitro using more complicated eukaryotic systems because the specification teaches that these mutants will not work for simple prokaryotic systems and provides no indication that the more complicated systems would work any differently.

[4] The Examiner agrees that the "entire disclosure" must be considered in accordance with MPEP §2164.08(c). However, the "entire disclosure" does not enable a person of skill in the art to make and use the claimed invention. Generic language (i.e., page 6, lines 5 to 9) coupled with examples of species that do not work within the genus (e.g., example 7) would not enable a person of skill in the art to make and use a sub-generic that is not explicitly referred to

(i.e., Applicants never refer to M182T, K55E and P62S mutants in vitro using eukaryotic systems, nor is any data provided on how these mutants would perform under those conditions).

[5] First, the Examiner notes that even if *assuming arguendo* Applicants' arguments were correct, it would not obviate the Enablement rejection because the Enablement rejection is not solely based upon the "criticality" of the "complimentary C-terminal β-lactamase fragment" (e.g., see above arguments). Second, the Examiner contends that Applicants claimed fragment ***could not be used*** in a complementation system without the complimentary C-terminal β-lactamase fragment. Thus, Applicants' current claim language requires the addition of the essential C-terminal β-lactamase fragment. In addition, the Examiner notes that Applicants have not been "denied" the opportunity to claim any single component because Applicants are not prevented from amended their claims to delete the current claim usage (i.e., "for use in a fragment complementation system").

Accordingly, the Enablement rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 63 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claim 63**, the phrase, "An oligopeptide for use in a fragment complementation system consisting essentially of an N-terminal β-lactamase fragment fused to a flexible polypeptide linker and a first interactor domain" is vague and indefinite. For example, it is not clear what "consisting essentially of" refers to? Does the phrase "consisting essentially of" refer to the N-terminal β-lactamase fragment (A) alone or does it refer to the β-lactamase fragment (A), linker (B) and first interactor domain (C) (i.e., does it refer A or A + B + C)? If it refers to the "N-terminal β-lactamase alone (i.e., only A) then Applicants would be using both "consisting essentially of" and "consisting of" to refer to the same protein fragment, which would be unclear (e.g., see claim 63 wherein Applicants state, "An oligopeptide ... consisting essentially of an N-terminal β-lactamase fragment ... wherein said N-terminal β-lactamase fragment consists of ...") because a person of skill in the art would not know what standard to apply (i.e., would the first transitional phrase broaden the second transitional phrase?).

In addition, the Examiner contends that "consisting essentially of" is generally used for "composition" and/or "method" claims (e.g., see MPEP § 211.03) and, as a result, it is not clear how this transitional phrase would be applied to a "compound" claim (i.e., the N-terminal β-lactamase fragment). Specifically, it is not clear if "consisting essentially of" would include "conservative substitutions" within the N-terminal B-lactamase fragment itself?

For example, the phrase "consisting of the N-terminal β-lactamase fragment" is clear because this transitional phrase is "closed" and thus would exclude therefrom any element or ingredient not specified in the claim i.e., only the exact N-terminal β-

lactamase fragment sequence would be encompassed (see MPEP § 2111.03). Likewise, the phrase "comprising the N-terminal β-lactamase fragment" is also clear because this transitional phrase is "open" and thus would include the N-terminal β-lactamase fragment (without any substitutions, mutations and/or deletions within the N-terminal β-lactamase fragment itself because this fragment is an "essential" element) AND any additional elements or ingredients (i.e., the addition of more amino acids to the 5'/3' ends of the sequence) (e.g., see Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential [i.e., the β-lactamase fragment is essential and, as a result, cannot be altered], but other elements may be added and still form a construct within the scope of the claim.). Thus, the phrase "consisting essentially of the N-terminal β-lactamase fragment" would have to occupy some "middle" ground between the "closed" and "open" transitional phrases mentioned above.

However, it is not clear what this "middle" ground would be with regard to a single compound (i.e., the N-terminal β-lactamase fragment) because there are only two possible alternatives (i.e., you either can add amino acids to the 5'/3' end or you can't, which have already been expressed by the "comprising" and "consisting of" terminology, respectively). Thus, if "consisting essentially of" the N-terminal β-lactamase fragment is to mean something different than "consisting of ..." (i.e., closed wherein only a single sequence is permitted) or "comprising ..." (i.e., open i.e., wherein an infinite number of sequences are permitted that "add" amino acids either to the 5' or 3' end) then the N-terminal β-lactamase fragment itself must possess "conservative substitutions" in order to

distinguish this transitional phrase from the closed/open terminology. Permitting "conservative substitutions" within the N-terminal β-lactamase sequence itself, however, would allow sequences to fall within the narrower scope of "consisting essentially of" that do not fall within the broader scope of "comprising" (e.g., sequences with conservative substitutions in the N-terminal β-lactamase fragment itself), which would appear to contradict MPEP § 2111.03 because the "consisting essential of" terminology would no longer occupy a "middle" ground with respect to the sequences that have conservative substitutions in the N-terminal β-lactamase sequence itself.

Additional References Relevant to the Invention

6. The examiner places the following reference on the record as being relevant to the presently claimed invention:

Michnick et al. (U.S. Patent Application 2003/0108869 A1) disclose, but does not claim, Applicant's currently claimed M182T mutant (e.g., see Michnick et al., Example 6), but fails to provide a priority date that antedates Applicants' 3/15/2000 filing date (e.g., see Michnick et al. wherein the earliest effective US filing priority date is **June 2, 2000**).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
August 31, 2004

BENNETT CELSA
PRIMARY EXAMINER